EXHIBIT 1: AMENDMENTS TO U.S. PATENT APPLICATION SERIAL NO. 09/863,765 (ATTORNEY DOCKET NO. 9373/1H812US2)

SUBMITTED PURSUANT TO 37 C.F.R. § 1.121(b)(1)(iii)

The paragraph at lines 9-11 on page 16 of the specification should be amended as follows:

FIG. 7 is an example of an *in vitro* method of overlap extension reassembly, targeting identified crossover locations. The appropriate fragments may be obtained by split-pool synthesis. In **FIG. 7**, part (A), all possible recombinants are prepared by crossover at positions 1 and 2. In **FIG 7**, part (B), the recombinants can be prepared by assembly of synthetic fragments containing the crossover positions. This example requires fragments (plus end primers).

The paragraph at lines 12-15 on page 16 of the specification should be amended as follows:

FIG. 8, part (A), [**A**]shows a fragment reassembly method using a parental template. The synthetic fragments are extended against a parent template strand and the gaps are repaired. In **FIG. 8**, part (B), t[T]he resulting products are subjected to heteroduplex recombination (Volkov *et al., Nucl. Acids Res.*, 27:18 (1999))to create libraries of genes within regions of non-identity. More complexity can be introduced by the addition of more fragments during template assembly.

The paragraph at lines 16-17 on page 16 of the specification should be amended as follows:

FIG. 9 shows the preparation of gene fragments prepared by PCR with primers directed to regions targeted for crossovers. In **FIG. 9**, part (A), the fragments are prepared by PCR with primers. The PCR reactions are performed with primers 1 + 2, 3 + 4 and 5 + 6. The method is repeated for the other parents.

The paragraph at lines 18-19 on page 16 of the specification should be amended as follows:

FIG. 10 shows recombination directed to specific sites using crossover primers in DNA shuffling. In **FIG. 10**, part (A), crossover primers designed to have crossovers at designated positions (2 primers for each position) are prepared. In **FIG. 10**, part (B), the parent genes are fragmented and reassembled , utilizing PCR methods, in the presence of the crossover primers to promote recombination at designated positions.

The paragraph at lines 22-23 on page 16 of the specification should be amended as follows:

FIG. 12 is a flow diagram illustrating one embodiment of a recombinant search algorithm of the invention, based upon sequence identity. In **FIG. 12**, part (1), the parent sequences are aligned with the template structure. In **FIG 12**, part (2), all

possible crossover points are determined according to a sequence identity algorithm. In **FIG. 12**, part (3), the coupling matrix is calculated. In **FIG. 12**, part (4), a start parent is picked at random and copied to the offspring until a possible cut point is reached. In **FIG. 12**, part (5), a random number is picked, and if the number is less than p, a random new parent is copied until the next cut point is reached. In **FIG. 12**, part (6), the crossover disruption of the offspring gene is determined.

The paragraph beginning at line 22 on page 17 of the specification should be amended as follows:

FIG. 19 is a schematic demonstrating the utility of a contact map in identifying compact units of substructure. A representative contact map is on the left. The graph on the right is a statistical study of the average length of contiguous residues that can fold into a sphere of the indicated diameter (Gilbert 1998). This information can be used in the following way. If a 15-residue segment can fold into a sphere with a diameter of 21 angstroms, then this segment could be considered as being of average compactness. However, if a 20-residue segment can fold into a sphere of 21 angstroms, this is considered as having a significantly above-average compactness. This is visualized on the contact map as a triangle on the diagonal formed by the cut points required to generate the segment. If the segment fits into a sphere of the specified diameter, then the triangle will be entirely white (interacting). The contact map shows residues that are distant (black) and residues that are close

(white). If a given segment, [redacted], folds an above average number of residues into a given sphere size, then it is compact.

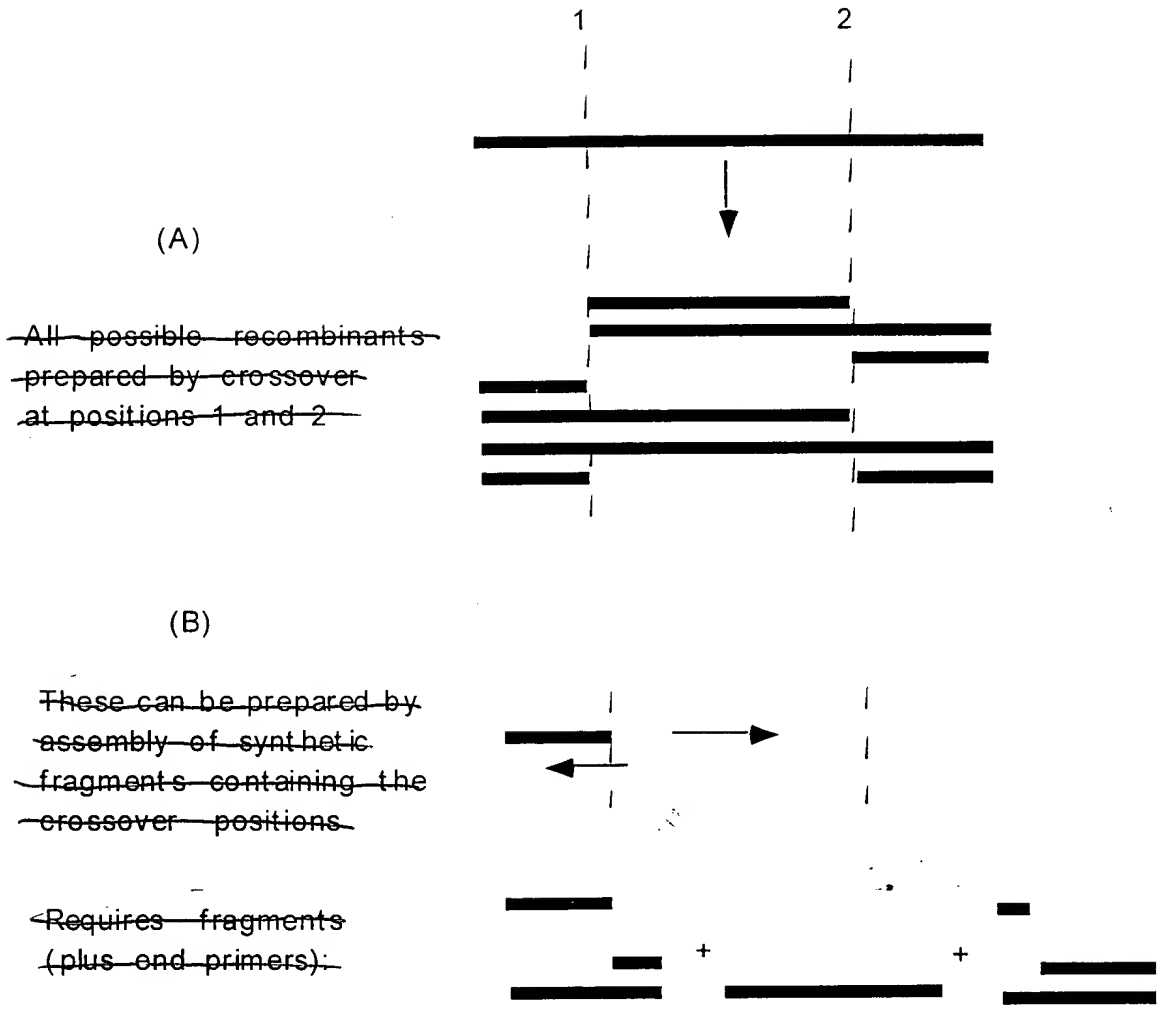

1
2
(A)
All possible recombinants prepared by crossover at positions 1 and 2
(B)
These can be prepared by assembly of synthetic fragments containing the crossover positions
Requires fragments (plus end primers):
+
+

FIG. 7

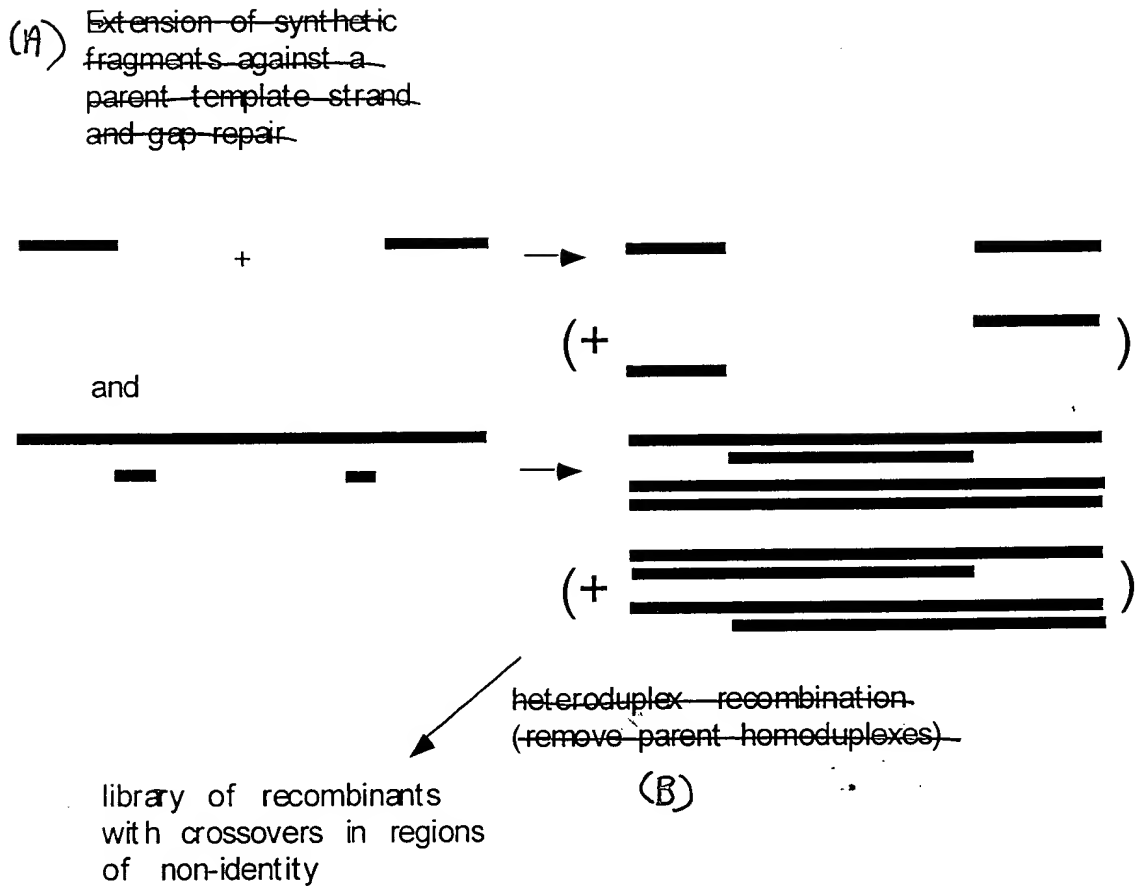

(A) Extension of synthetic fragments against a parent template strand and gap repair
+
(+)
and
(+)
heteroduplex recombination (remove parent homoduplexes)
(B)
library of recombinants with crossovers in regions of non-identity

FIG. 8

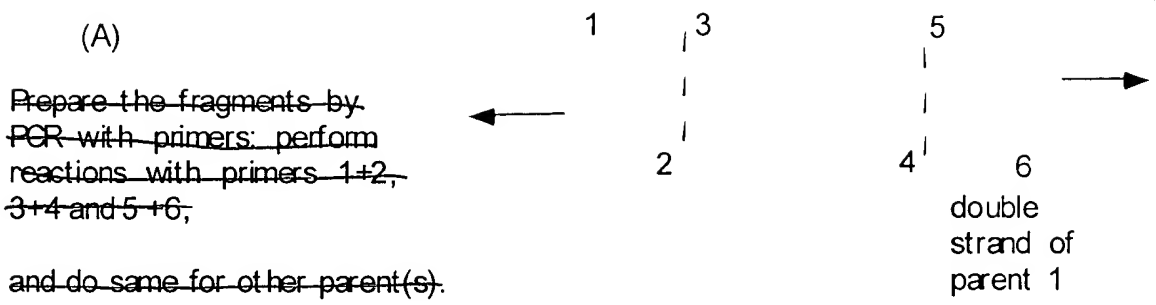

(A)
Prepare the fragments by PCR with primers: perform reactions with primers 1+2, 3+4 and 5+6;
and do same for other parent(s).
1
3
2
5
4
6
double strand of parent 1
(B)
Reassemble fragments in a pool, by PCR with 1+ 6

FIG. 9

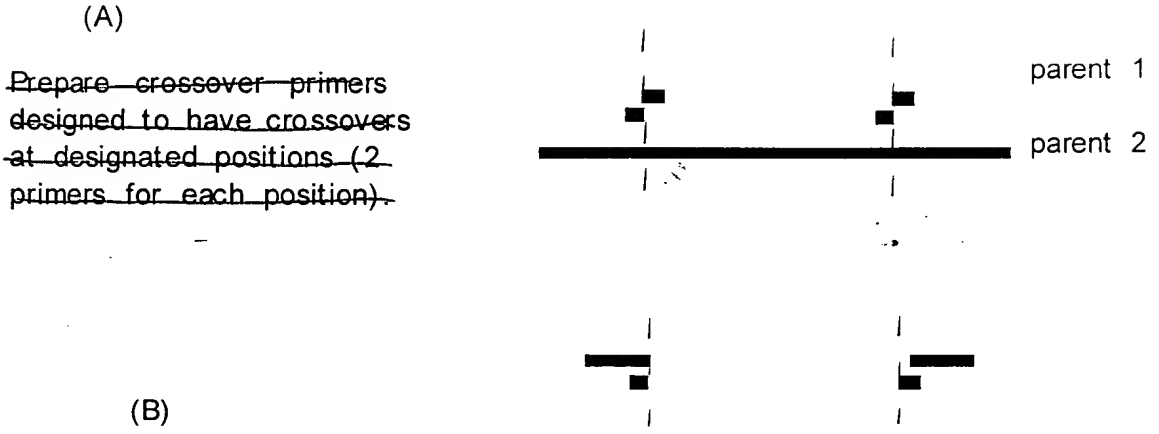
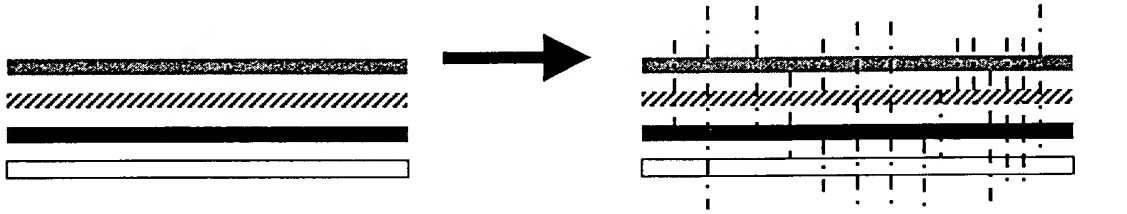

(A)
Prepare crossover primers designed to have crossovers at designated positions (2 primers for each position).
parent 1
parent 2
(B)
Fragment parent genes and PCR reassemble in the presence of the crossover primers to promote recombination at designated positions

FIG. 10

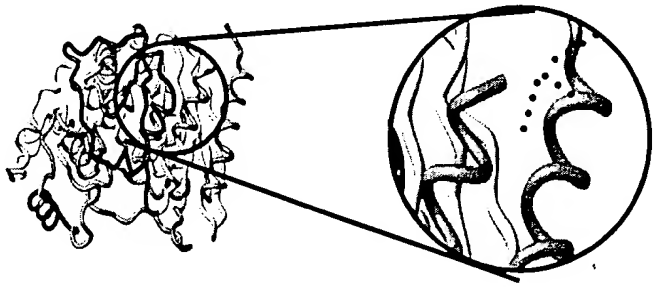
Recombinant search algorithm

1. Align parent sequences with template structure

2. Determine all possible crossover points according to sequence identity algorithm

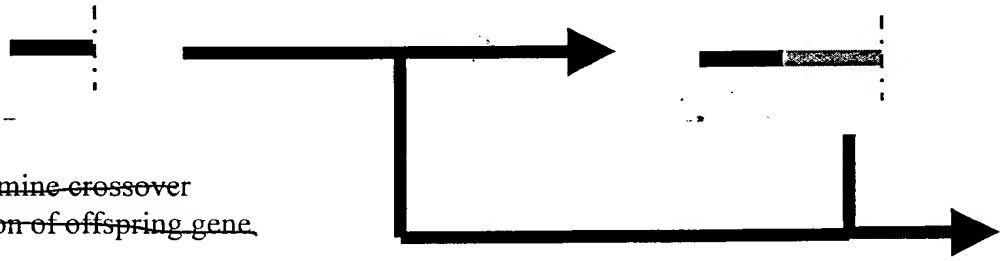


3. Calculate coupling matrix



4. Pick start parent at random and copy to offspring until a possible cut point is reached

5. Pick random number, if less than *p*, copy random new parent until next cut point is reached.



6. Determine crossover disruption of offspring gene.

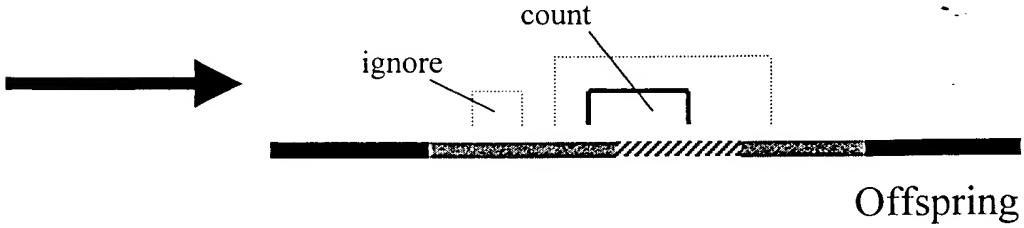


FIG. 12

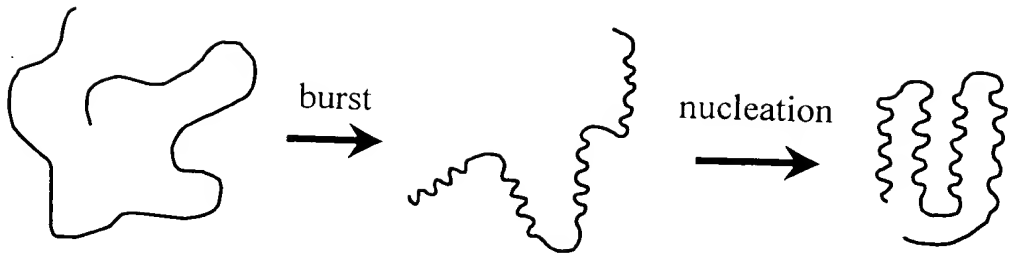


FIG. 18

~~The contact map shows residues that are distant (black) and residues that are close (white). If a given segment, [redacted], folds an above average number of residues into a given sphere size, then it is compact.~~

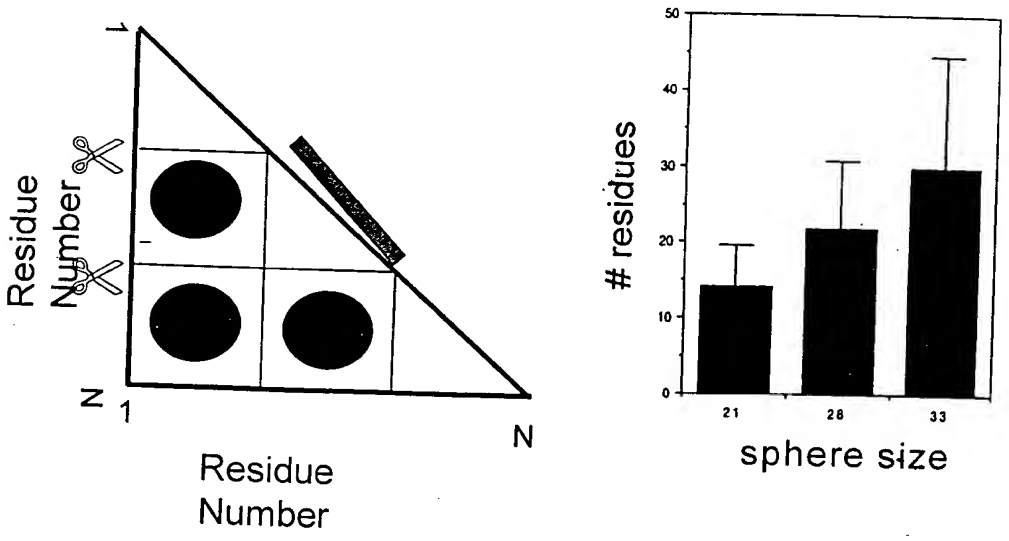


FIG. 19

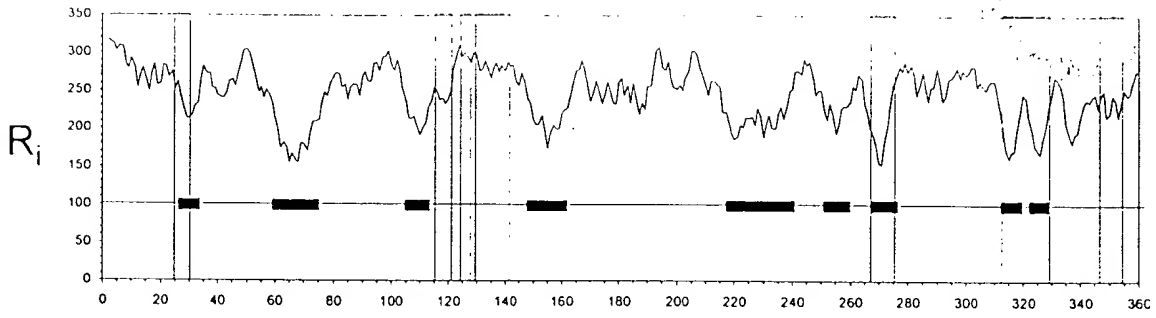
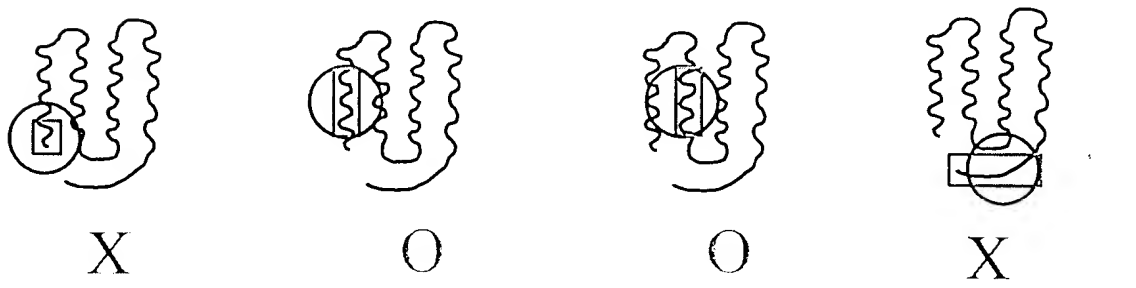


FIG. 22



~~(1) Pick a sphere size (21 angstroms, like Go-Gilbert) and a disruption threshold; (2) Scan protein using segments at least the average number of residues for that sphere size or greater (e.g., >15 for 21 angstrom sphere); 3) Check the disruption of all the compact fragments identified in step 2. If the fragment has a disruption above a threshold value, keep it; otherwise, throw it out; 4) If the compact unit is disruptive, increment the schema disruption measure for all of the residues in the fragment by one. This indicates that crossovers within the fragment are disfavored.~~

FIG. 23